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PATENT APPLICATION
Attorney's Docket No.: 3518.1012-005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mohamed Attawia, Hassan Serhan, Thomas M. DiMauro, Melissa Grace and David Urbahns		
Application No.:	10/714,594	Group:	1649
Filed:	November 14, 2003	Examiner:	Steven H. Standley
Confirmation No:	3230		
For:	Autologous Treatment of Degenerated Disc With Cells		

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DECLARATION OF MOHAMED ATTAWIA, M.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mohamed Attawia, M.D. of Eatontown, New Jersey hereby declare that:

1. I am currently Vice President of Osteotech Inc. in Eatontown, New Jersey. I have been employed at Osteotech Inc. since 2007. I was previously employed at DePuy Acromed (Currently "DePuy Spine") and DePuy Biologics.

2. I am an inventor of the subject matter described and claimed in U.S. Patent Application No. 10/714,594 filed on November 14, 2003 entitled "Autologous Treatment of Degenerated Disc With Cells" assigned to DePuy Spine Inc. ("the '594 application").

3. I received my M.D. from School of Medicine, Cairo University, Cairo, Egypt. I have published and lectured extensively, primarily focusing on tissue engineering and bone

repair, specifically spinal disc repair, for approximately 20 years. A copy of my *curriculum vitae*, which describes my educational and professional experience and publications I have authored, is attached.

4. To prepare this Declaration, I have been asked to comment on the invention described in the patent application and the primary reference cited in the pending Office Action for the '594 application, Sakai *et al.*, *Biomaterials, 24*: 3531-41 (2003) ("Sakai *et al.*").

5. To prepare this Declaration, I have read the above-identified U.S. Patent Application No. 10/714,594, the Office Action issued by the United States Patent and Trademark Office (PTO) on December 28, 2007, and Sakai *et al.*

6. The present invention is directed to treatment of degenerative disc cells in an intervertebral disc by administering autologous uncultured mesenchymal stem cells (MSCs) into a degenerated intervertebral disc.

7. At the time of the invention, it was general knowledge that mesenchymal stem cells (MSCs) are pluripotent cells found in the body in extremely small numbers.

8. Therefore, persons of skill in the art believed that expansion of the cells by culturing was required before transplantation. This culturing led to a number of difficulties, including requiring two separate operations (one for harvesting the cells from the patient, and then another for administering the cells to the patient after the cells are cultured). It also led to the possibility of impurities, contamination and exposure to additives in the cultured cell line.

9. Therefore, there has been a long-felt, but unsatisfied need to improve the effectiveness of treatment for degenerative disc disease.

10. The current invention is based on the development of a procedure for treating degenerative disc disease by administering uncultured autologous MSCs using the methods described in the present application.

11. Sakai *et al.* neither teach nor suggest administration of uncultured MSCs to a patient.

12. Sakai *et al.* teach administering cultured cells from the outset because Sakai *et al.*'s preferred mode of cell delivery requires cell culture expansion. Sakai *et al.* had two reasons for culturing the cells: (1) to label the MSCs; and (2) to use Atelocollagen® gel as a carrier for the MSCs.

13. Specifically, Sakai *et al.* teach culturing the cells for 12-15 days (Sakai *et al.*, Section 2.1.), labeling the cultured cells (Sakai *et al.*, Section 2.2), and embedding the cells in liquid Atelocollagen® gel solution while culturing the cells in Atelocollagen® gel solution (Sakai *et al.*, Section 2.4.). Sakai *et al.* taught that this last step was an important part of his study, noting at page 3532, first complete paragraph: "Basic science research on culturing chondrocytes in Atelocollagen® gel has shown that cultures using Atelocollagen® gel result in greater matrix synthesis when compared to cells cultured in monolayer" and at page 3538, first paragraph, where it is recited: "In order to use in cell cultures, Atelocollagen® solution was neutralized by adding HEPES buffer (pH 7.4) and $NaHCO_3$."

14. Using the matrix gel, Atelocollagen® gel, as a mode of delivery required Sakai *et al.* to attach the MSCs to the three-dimensional matrix of the gel carrier at a higher number. This process of attachment requires time and culturing of the MSCs during the formation of the solid matrix from the liquid solution. Therefore, Sakai *et al.*'s method requires cell culture expansion in order to create an effective matrix with a high number of the MSCs successfully attached.

15. Further, references cited favorably by Sakai *et al.* also teach the cell culture step (see, *e.g.*, Sakai *et al.*: Reference Nos. 28-33). Specifically, Sakai cites these references as examples of therapeutic uses of MSCs other than spinal disc repairs. In particular, I am familiar with the research of the cited authors, Caplan and Haynesworth. Similar to Sakai *et al.*'s method, their methods involve cell culture expansion, because it was a common consensus among the scientists in the field that cell culture expansion was required for the effective administration of the MSCs for treatment.

16. If Sakai *et al.*, Caplan *et al.* and Haynesworth *et al.* contemplated that administering uncultured cells is an obvious improvement over the methods, they would have taught their methods as a control to show the benefits of uncultured cells in therapy. In other words, one of skill in the art would design such a study to have several test groups, including a group where cells are cultured and another group where the cells are not cultured.

17. In addition, it was well known in the field that *ex vivo* cell culture is highly susceptible to various types of contamination (*e.g.*, viral, bacterial, and/or fungal) and that such contamination would greatly increase the risk of contamination in clinical therapy. Further, *ex vivo* cell cultures requires the addition of chemical additives to the culture medium (*e.g.*, antibiotics, etc.), exposing the cells to such additives. Therefore, if Sakai *et al*, Caplan *et al.* and Haynesworth *et al.* had contemplated administration of uncultured stem cells as an obvious improvement, they would have assessed the risk of culturing the cells by comparing the *in vivo* outcome of administration of uncultured versus cultured cells. The fact that none of these references ever suggested testing the outcomes of administering cultured versus uncultured cells demonstrates that the claimed method was not obvious at the time of the invention.

18. At the time of the invention, it would have not been obvious to the scientists of ordinary skill in the art of regenerative medicine that administering uncultured MSCs would lead to clinical efficacy, because the number of MSCs available in the bone marrow was

known to be extremely scarce. This concept is supported by Centeno *et al.* (see Centeno *et al.*, *Pain Physician* 11(3): 343-353 (2008); Attached as Exhibit A), who study regenerative medicine for joint and cartilage diseases. Centeno *et al.* state that: "these techniques produce a very dilute MSC population, usually a yield of 1 out of 10,000-1,000,000 bone marrow nucleated cells…As discussed above, the number of MSCs that can be isolated from bone marrow is limited" (see *Id.* at page 345, col. 2). As a result, Centeno *et al.* state that: "most research in cartilage regeneration has focused on the use of cultured expanded cells" (see *Id.* page 345, left column 1st and 2nd paragraph, *emphasis added*). To this end, Sakai *et al.* also states that: "MSCs are undifferentiated cells found in small numbers in the periosteum or in the bone marrow" (Sakai *et al.*, page 3532, left col., 4th full paragraph, *emphasis added*). Therefore, it would not have been obvious at the time of the invention that one could treat a degenerated intervertebral disc by administering autologous uncultured MSCs.

19. I further declare that all statements made herein are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Mohamed Attawia

6/26/08

Date

Attachments:

curriculum vitae

Exhibit A